

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Kantamneni, Shobha
Art Unit : 1617
Applicants : Kivlighn et al.
Serial No. : 09/892,505
Filed : June 28, 2001
For : Treatment For Cardiovascular Disease

SECOND DECLARATION OF RICHARD JOHNSON, M.D.

I, Richard Johnson, hereby declare and say as follows:

THAT, I am employed as a Professor of Medicine at the University of Florida, Gainesville, FL.;

THAT, I am one of the above-named Applicants and inventors of the subject matter described and claimed in the above-identified patent application;

THAT, by virtue of my educational and employment background, my attendance at seminars, my ongoing research, my continuing review of scientific periodicals and journals, and through correspondence with professional colleagues, I am aware of the level of skill of one ordinarily skilled in the art of cardiovascular disease and kidney disease, and in particular, mechanisms of hypertension;

THAT, I have studied the application Serial No. 09/892,505 and office actions which have been issued during prosecution of this application (including cited references), as well as responses which have been filed on the Applicants' behalf, and being thus duly qualified declare as follows:

1. I have studied the Nakamoto European patent (Nakamoto Patent) cited by the Examiner in the subject application. The Nakamoto patent is directed to a new uricosuric compound; not to a xanthine oxidase inhibitor. However, the Nakamoto patent makes one statement that the U.S. Patent Office relies on for its allegation that Nakamoto discloses that compounds which reduce uric acid are effective in curing hypertension¹. Nakamoto reasons that if gout is associated with hypertension, then curing gout with its uricosuric compound will cure hypertension (page 7, lines 55). This reasoning in the

Nakamoto reference is so defective from a medical/scientific perspective that even a person with little skill in the art would immediately reject it. Those trained in science and medicine are careful not to confuse association with causation. The Nakamoto patent authors clearly make this mistake. As an example, let's assume that a study finds that smoking is associated with liver cirrhosis. Those skilled in the art would not conclude from this that smoking causes liver cirrhosis (rather the medical community would undoubtedly interpret this study to mean that many people who smoke also drink). The only way to determine whether smoking causes liver cirrhosis or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study. I note that Nakamoto provides zero supporting data or evidence to support its reasoning.

2. To my knowledge, there have never been any clinical trials using the Nakamoto uricosuric compound. Had those skilled in the art thought that the Nakamoto uricosuric compound could cure or prevent hypertension by lowering uric acid, certainly there would have been studies to test the compound for this purpose or studies testing other known uricosurics. However, the scientific and patent literature reveals that the Nakamoto patent was not accepted as presenting a cure for hypertension, whether by administering its uricosuric compound or otherwise. A literature search in the PubMed database and a patent search of the USPTO database using the authors' names (and U.S. Counterpart 4,883,821) identified no citations to their work. In contrast, members of the famous Framingham Heart Study group, experts in the field of hypertension, declared in 1999 (note that the Nakamoto patent was issued in 1991) that uric acid does not play a causative role in hypertension², such conclusion being supported by a comprehensive scientific study.

3. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information in belief are believed to be true; and further that these statements were made with the knowledge that willful false statements in the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the U.S.C. and that such willful false statements made jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

A handwritten signature in black ink, appearing to read 'Richard Johnson', with a stylized, flowing script.

Richard J Johnson, M.D.
Professor and Chief,
Division of Nephrology, Hypertension and
Transplantation
University of Florida
Oct 27th, 2007

1. The Nakamoto patent states that its diuretic compound “is effective in curing gout by ameliorating and curing hyperuricemia. This disease often accompanies hypertension, arteriosclerosis and myocardial infarction because of characteristics of the disease. Accordingly, the compound of the present invention is effective in curing or preventing hypertension, arteriosclerosis or myocardial infarction accompanied by hyperuricemia.” (page 7, line 55-59)

2. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7-13.